# Modeling the Dynamics of the RIG-I-MAVS/ NF-κB/IRF3 Signaling Pathway

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***Short Abstract* — RIG-I-MAVS complex plays an active role in recognition of viral RNA, initiating a cascade of signaling pathways leading to the production of the cytokine Interferon-β, and inflammatory response through the activation of NF-κB. We have performed experiments and developed a preliminary stochastic model of the dynamics of the pathway, which will allow us to predict the module's response to a range of hypothetical experimental conditions.**

***Keywords* — Innate immunity, Modeling, RIG-I-MAVS, IRF3, NF-κB,.**

## I. Purpose

Double- and single-stranded viral RNAs bind to Cytoplasmic Retinoic acid-Inducible Gene 1 (RIG-I) inducing its ubiquitylation. This complex then binds to Mitochondrial Anti-Viral Signaling protein (MAVS; also known as IPS-1, VISA, and CARDIF). This oligomer, known as RIG-I-MAVS, recruits TNF Receptor-Associated Factors (TRAFs) 2, 3 and 6. The resulting complex generates divergent signaling pathways that control two potent transcription factors: NF-κB and IRF3 [1].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a gene regulatory protein, or a transcription factor (TF). NF-κB is a key player in many stress-induced inflammatory and innate immune responses. In unstimulated cells, NF-κB is in a dormant state, sequestered in the cytoplasm by a family of inhibitors, mainly by the Inhibitor of κB α (IκBα). When an external stimulus (such as Tumor Necrosis Factor α, or TNFα) activates specific receptors, the IκB Kinase (IKK) becomes activated, subsequently phosphorilating IκBα and leading to its degradation. The freed NF-κB then enters the nucleus, activating a number of target genes. Among them, at least two are important for regulation of NF-κB itself: A20 and IκBα. A20 inactivates IKK, and IκBα binds NF-κB inhibiting its action.

Activated IRF3 migrates into the nucleus, where it forms and enhansome with NF-κB [2], activating the production of type I interferons (IFNs), which in turn generates potent up-regulation of RIG-I, which potentiates coordinated signaling by the NF-κB and IRF3 innate signaling responses [1].

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## II. Proposed Model

The current version of the proposed model consists of 62 chemical species and 73 reactions. The model can be separated into four modules summarized below:

1) Single-stranded viral RNA recognition by RIG-I-MAVS and recruitment of proteins, creating the oligomers that drive the divergent signaling pathways of IRF3 and NF-κB. Based on Liu et al. [1]. 2) IRF3 activation with resulting interferon production. Based on Liu et al. [1] and Ford and Thanos [2]. 3) RIG-I up-regulation as a response of interferon production. Based on Smieja et al. [3]. 4) NF-κB signaling pathway that produces inflammatory response (Groβ protein) and auto-regulatory proteins IκBα and A20, where the latter also down-regulates the RIG-I-MAVS pathway. Based on Lipniacki et al. [46,47], and Lipniacki and Kimmel [45].

## III. Experiments

Experiments, using cells directly infected with viral RNA, are under way. Time series of measurements, in 11 time points - from 2 to 36 hours post infection of mRNA transcript concentration of the IFNβ, RIG-I, IκBα, A20, and Groβ genes have already been performed in Brasier laboratory (UTMB). The mRNA series are being followed by similar time series of protein concentration for RIG-I, TRAF3, TRAF2/6, IKKγ-WT, IIKγΔ, IRF3, and IRF3pn and the complexes IKK -TBK1, IKKγ-WT-A20, IIKγΔ-A20. This will allow us to fine tune the parameters and validate the structure of the network proposed. In addition, we plan a range of knock-out experiments to separate the submodules of the RIG-I-MAVS pathway.

## References

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